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TITLE: Breast Cancer Risk in Relation to Serum IGF-1, IGFBP-3,
and Their Genetic Determinants: A Study Within the
European Prospective Into Cancer (EPIC)

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| 13. ABSTRACT (Maximum 200 Words) Purpose and scope: We are conducting a large case-control study nested within a prospective cohort, to estimate relative risks of breast cancer by serum levels of IGF-I and IGFBP-3, and to examine associations of polymorphisms in 15 candidate genes with levels of IGF-I, IGFBP-3, and cancer risk. Progress report: in the first two years of this project, 1084 breast cancer cases and 2116 control subjects were included in the study, and measurements of IGF-I and IGFBP-3 were (practically) completed. A first series of 23 SNPs were typed for all case and control subjects, and typing of 18 additional SNPs is ongoing. Major findings: Elevated serum IGF-I shows a moderate increase in breast cancer risk among postmenopausal women. Preliminary analyses also show significant associations of a number of SNPs and haplotypes with IGF-I, IGFBP-3, or breast cancer risk. | | | | |
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INTRODUCTION

IGF-I is a central hormone in the regulation of anabolic (growth) processes as a function of available energy and elementary substrates (e.g., essential amino acids), and has strongly mitogenic and anti-apoptotic activities. Results from *in vitro* studies and animal experiments show that, in excess, the anabolic signals by IGF-I can promote the development of tumors at various organ sites, and recent epidemiological studies have shown an increased breast cancer risk in women with elevated serum IGF-I, or with elevated levels of IGF-I for given levels of IGFBP-3, the major plasmatic IGF-binding protein.

While nutritional status is one important determinant of circulating IGF-I levels (Kaaks & Lukanova, 2001), heritability studies have shown that, in well-nourished populations, a large part (40-60 %) of variation in IGF-I is (co)determined by genetic factors (Harrela et al., 1996; Hong et al. 1996; Verhaeghe et al., 1996). To increase understanding of what are the major determinants of IGF-I levels, as well as cancer risk, we conduct a study with the following objectives:

1. Confirm that elevated prediagnostic serum levels of IGF-I increase breast cancer risk, especially in premenopausal women;
2. Describe exhaustively existing polymorphisms, allele frequencies and haplotypes in 15 selected genes related to the secretion of growth hormone, and hence to the synthesis of IGF-I and IGFBP-3; and
3. Examine whether these genetic polymorphisms are related to significant increases or decreases in circulating levels of IGF-I and IGFBP-3, as well as in breast cancer risk.

Our project is a large case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC), using prediagnostic blood (serum and DNA) samples collected during 1992-1998, from 233,800 women in western Europe.

As mentioned in our original application, the study was planned in four parts:

1. A case-control study (about 1000 cases and 1000 controls) nested in a prospective cohort, to estimate the associations of serum IGF-I and IGFBP-3 levels with breast cancer risk;
2. Preparation of an exhaustive catalogue of polymorphisms and haplotypes in the 15 selected candidate genes, and a ("phase-1") association study on a subset of 400 controls to identify genotypes that have a minimum level of association with serum of IGF-I and IGFBP-3;
3. A nested case-control study, to estimate relative risks of breast cancer in relation only to those genotypes selected in phase-1;
4. A ("phase-2") study of associations of these selected genotypes with IGF-I and IGFBP-3, in all cases and controls.

BODY

For **Year 1**, our workplan (as in the "Statement of Work" section of our application), was as follows:

1. Selection of cases and controls, using the established eligibility and matching criteria, and extraction of case-control data sets with relevant information from questionnaires and anthropometry: **Task 1, months 1-2.**
2. Retrieval of serum and buffy coat samples from the central EPIC storage facility; assembly of the serum samples into batches of matched case-control sets for immunoassays; assembly of the buffy-coat samples into batches for DNA extraction: **Task 2, months 2-4.**
3. Assays of IGF-I and IGFBP-3 serum of breast cancer cases (n = 1000) and controls (n = 1000): **Task 3, months 7-12.**
4. DNA extraction for all 2000 cases and controls: **Task 5, months 1-12.**
5. Preparation of an exhaustive catalog of polymorphisms by searching the literature, and by DHPLC analysis of DNA from a subset of 200 subjects: **Task 6: months 1-12.**

As described in our previous report (Year 1), we achieved most of these goals in Year 1, whereas for some other tasks we were in advance of our planned schedule. The following list provides a quick recapitulation of key accomplishments in Year 1:

- a) Case-control selection, DNA extraction, and growth factor measurements:
 - An almost complete selection of breast cancer cases (n=810) and control subjects (n=1620) within the EPIC cohorts, for the nested case-control study on serum IGF-I, IGFBP-3 and breast cancer risk;
 - Measurement of IGF-I and IGFBP-3 for these cases and controls;
 - DNA extraction for these cases and controls;
- b) Preparation of SNP genotyping tools:
 - Identification of a comprehensive catalogue of >120 (possible) single nucleotide polymorphisms (SNPs) in all candidate genes included in the present study;
 - Preparation of a DNA genotyping chip, for 78 of these polymorphisms that had confirmation of being true polymorphisms;
- c) Preliminary genotyping study:
 - A first descriptive study of SNP and haplotype frequencies for all candidate genes, in a population of 477 subjects (women plus men); and
 - A preliminary analysis of associations of SNPs and circulating levels of IGF-I and IGFBP-3 (corresponds to **Task 7**, originally planned for Year 2);
 - Selection of a first series of 23 SNPs to be typed in the full case-control study, using the Taqman assay.

During **Year 2**, we completed some of the tasks originally planned for Year 1. In particular, we included 274 cases of breast cancer and 496 control subjects, for whom questionnaire information available in 2002 did not allow proper control matching (this information arrived during 2002). Thus, total numbers of breast cancer cases and control subjects were brought to 1084 and 2116, respectively.

For these additional study subjects, DNA was extracted from their stored buffy coat specimens, and additional serum measurements of IGF-I were performed. For IGFBP-3, measurements were delayed because of technical difficulties with the (commercial) assay, due to complications at the manufacturing site (DSL, TX, USA). In collaboration with the company, these problems have now been solved, and completion of the IGFBP-3 assays is scheduled for September-October 2003.

Tasks planned for Years 2 and 3 ("Statement of Work" section of our study proposal) were:

6. Statistical analysis of the nested case-control study, relating breast cancer risk to prediagnostic serum levels of IGF-I and IGFBP-3 (**Task 4, months 13-24**);
7. Complete genotyping of a subset of 200 breast cancer cases and 200 control subjects; Statistical analysis of phase-1 association study, relating genotypes to serum concentrations of IGF-I and IGFBP-3 (**Task 7; months 12-24**); and
8. Genotyping of the remaining 1600 cases and controls, for a limited set of polymorphisms, selected in phase 1;

Statistical analysis of associations between polymorphisms, serum levels of IGF-I and IGFBP-3, and breast cancer risk; Writing of reports (**Task 8; months 24-36**).

All of the goals up to the end of Year 2, and much of the goals for Year 3, have been met:

- (a) Statistical analysis of breast cancer risk in relation to prediagnostic serum levels of IGF-I and IGFBP-3 (Task 4):

Although IGFBP-3 measurements are not complete yet (see above), we performed extensive statistical analyses of the relationships of breast cancer risk with serum IGF-I and IGFBP-3 concentrations. These analyses showed no clear relationship of breast cancer risk with IGF-I among women who were premenopausal at the time of blood donation, contrary to findings from some previous cohort studies. Among postmenopausal women, however, there was a moderate association of risk with IGF-I (relative risk of about 1.5 between the extreme quintiles of the IGF-I exposure distribution).

- (b) Further SNP genotyping of breast cancer cases and control subjects (Task 8):

For all 1084 breast cases and 2116 controls included in the nested case-control study, a first series of 23 SNPs were typed by Taqman. For an additional number of SNPs, genotyping assays by the Taqman technique did not work (a normal observation with this type of assay); for these, we are currently trying to set up alternative assays (e.g., "Amplifluor"). For yet another set of SNPs, our DNA chip initially used for genotyping in a smaller subset of individuals (total of 78 SNPs) did not give valid

results, and we were thus unable not confirm whether or not polymorphic alleles were prevalent enough to make their measurement worthwhile. For this latter subset, we have now decided to type all of these SNPs by Taqman or the Amplifluor technique. In total, some 18 SNPs remain to be typed for all case and control subjects, which will bring the total number of SNPs typed to 41. This total number of assays (SNPs) is considerably larger than that foreseen in our original study proposal; however, genotyping of this increased number largely has become possible due to the progressive reductions in genotyping reagent costs.

(c) Statistical analysis of SNP / haplotype associations with IGF-I and IGFBP-3 (Tasks 7 and 8):

In Year 1, performed preliminary statistical analyses were performed to examine possible associations of SNPs and their haplotypes with serum concentrations of IGF-I and IGFBP-3, within a first series of 477 subjects (see our previous report).

During Year 2, we re-analysed our much more extensive data, from all 1084 breast cancer cases and 2116 controls, using the same methods as in Year 1.

Analyses were performed with a variety of statistical models, of increasing completeness and complexity:

- at the level of individual SNP loci: associations of alleles with IGF-I and IGFBP-3 concentrations were estimated under assumption of dominance, codominance, or recessiveness of alleles.
- at the level of full gene loci: individuals' most likely haplotypes were estimated, and individuals' haplotype combinations (of the two chromosomes) were associated with IGF-I and IGFBP-3 levels; in further analysis, haplotypes were transformed into SNP genotypes sorted by parental phase, and generalized linear models (GLM) were used to relate phenotype (IGF-I, IGFBP-3) to these phased genotype variables, plus their possible interaction terms within a gene (following an approach described by Cordell and Clayton, 2001).

During Year 2, we have also been working further on refinements of the statistical analysis procedures, implementing several new procedures (programmed in SAS), and testing different existing programs for estimation of haplotypes ('Arlequin'; 'PHASE'; 'SAS-Genetics'; TagSNP). A final analysis will be performed when genotyping of all 41 SNPs will be completed (planned to be complete by the end of 2003). Only after completion will it be possible to estimate full haplotypic variation at gene loci, and to perform definitive analyses.

Preliminary analyses of Year 1 suggested that up to some 20% of the total between-subject variation in IGF-I levels might be explained by measured genetic polymorphisms. This percentage was most likely overestimated, due to a comparatively small study size and over fitting of statistical models. Our current analyses, based on much larger numbers of observations, show smaller, but probably more realistic effects of SNPs and/or haplotypes on serum IGF-I and IGFBP-3 levels. Amongst the most significant associations was the relationship of IGFBP-3 levels with SNPs in the IGFBP-3 gene, which has also been observed in other studies (Jernström et al., 2001).

(d) Statistical analysis of SNP / haplotype associations with breast cancer risk (Task 8):

Preliminary statistical analyses have been performed, using logistic regression models to relate breast cancer risk to SNP genotypes as well as to haplotypes. The analytical strategy is similar to that for the analysis in relation to serum IGF-I and IGFBP-3 concentrations (described above). In addition, we have implemented a series of models to estimate haplotype relative risks, for a haplotype 'dosage' estimated as posterior probability for each of the possible haplotypes given SNP genotypes (following methods described by Stram et al., 2003).

A definitive statistical analysis of breast cancer risk in relation to SNP genotypes and, especially, haplotypes will be possible only after completion of genotyping for all 41 SNPs (by the end of 2003).

KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments in Year 2 were:

- Inclusion in the study of 274 additional breast cancer cases and 496 additional control subjects, bringing the total number of cases and controls to 1084 and 2116, respectively;
- DNA extraction and genotyping of a first series of 23 SNPs, for all cases and controls;
- IGF-I measurements for all cases and controls; nearly complete measurements of IGFBP-3.
- Extensive preliminary statistical analyses of associations between breast cancer risk, prediagnostic serum levels of IGF-I and IGFBP-3, and SNP and haplotype data; Preparation of programs and SAS macros for all analytical steps, ready to be implemented when all laboratory analyses will be completed.

PLAN FOR YEAR 3

Plans for Year 3 are as follows:

- Completion of genotyping of the 18 additional SNPs identified, and selected for the study;
- A definitive statistical analysis of the complete SNP genotype and haplotype data, in relation to serum IGF-I and IGFBP-3, as well as breast cancer risk;
- Preparation of articles, to report all major findings in scientific journals.

REPORTABLE OUTCOMES

None, so far. First drafts of articles are in preparation; these will be finalized after completion of all laboratory assays for genotypes and IGFBP-3, and definitive statistical analysis.

CONCLUSIONS

Our study is ahead of schedule, and actually has been expanded to include a larger number of SNP assays than initially foreseen (made possible because of decreasing genotyping costs). Results so far do indicate a number of associations of IGF-I, IGFBP-3 and breast cancer risk with SNP genotypes and/or haplotypes for full gene loci. The overall proportion of between-person variance in circulating levels of IGF-I and IGFBP-3 explained by the genetic polymorphisms is modest, however, but is still based on rather incomplete SNP and haplotype data.

Elevated serum IGF-I concentrations show a modest increase in breast cancer risk, but only among postmenopausal women.

Final statistical analyses of associations between breast cancer risk in relation to IGF-I, IGFBP-3, and genetic variants will be performed in Year 3, after the completion of the IGFBP-3 assays and additional SNP genotyping.

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APPENDICES

Tables with preliminary results from statistical analyses

Figure 1. Relative risk of breast cancer by quintiles of growth hormone levels

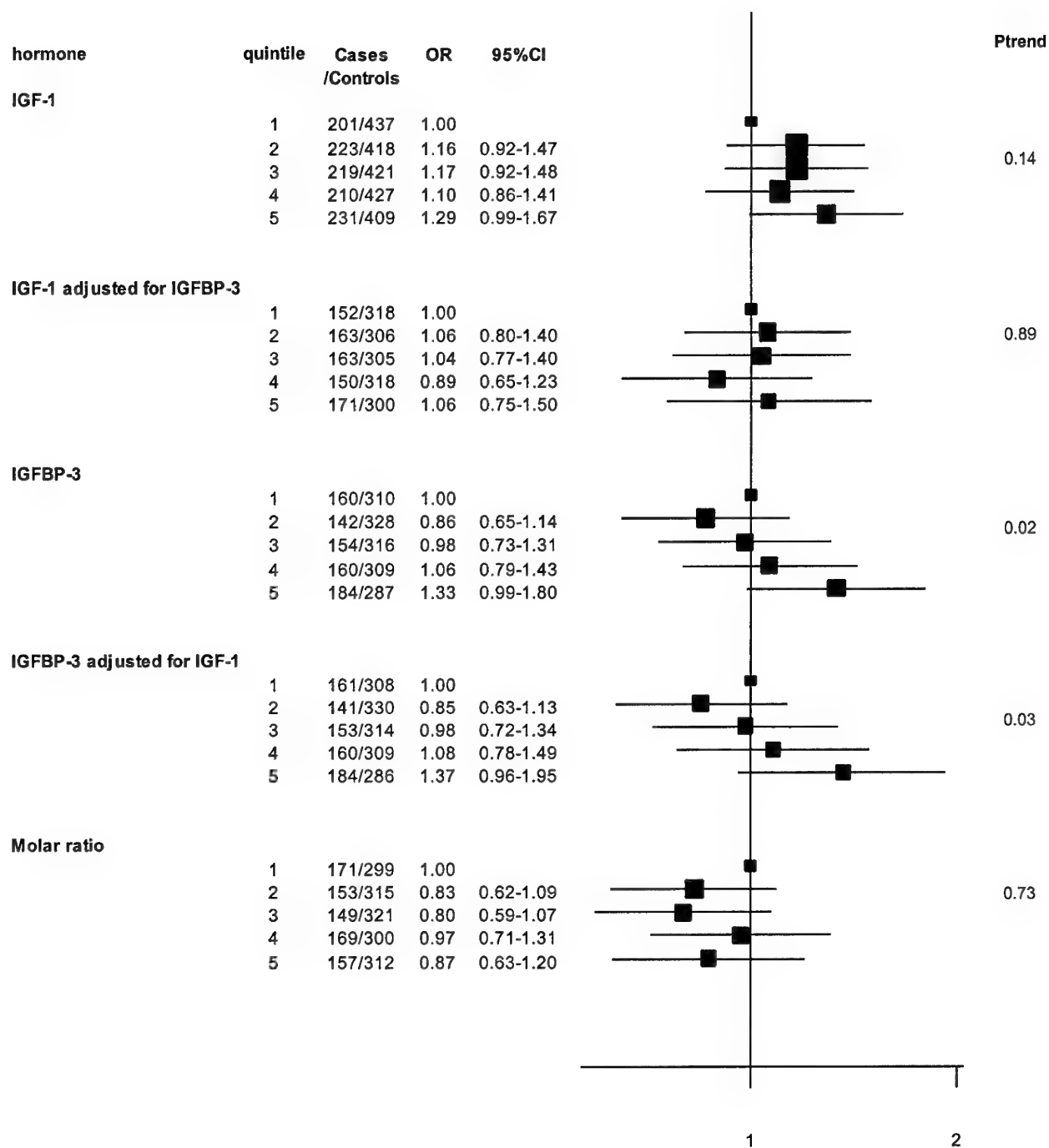


Figure 2. Relative risk of breast cancer among premenopausal women by quintiles of growth hormone levels

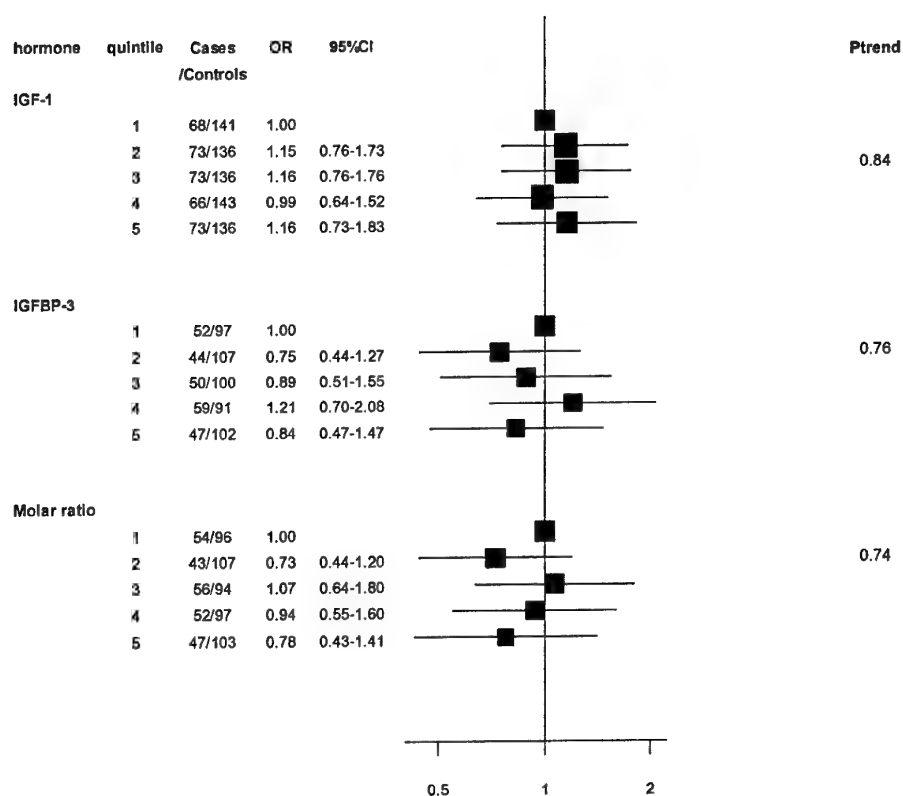


Figure 3. Relative risk of breast cancer among postmenopausal women by quintiles of growth hormone levels

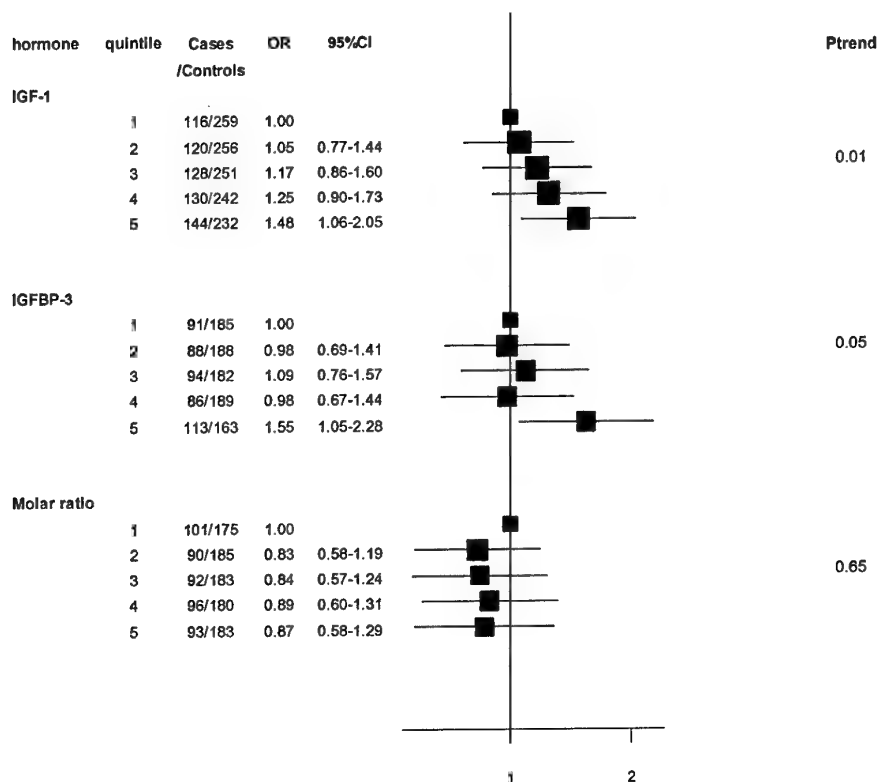


Figure 4. Relative risk of breast cancer among women younger than 50 at diagnosis at diagnosis by quintiles of growth hormone levels

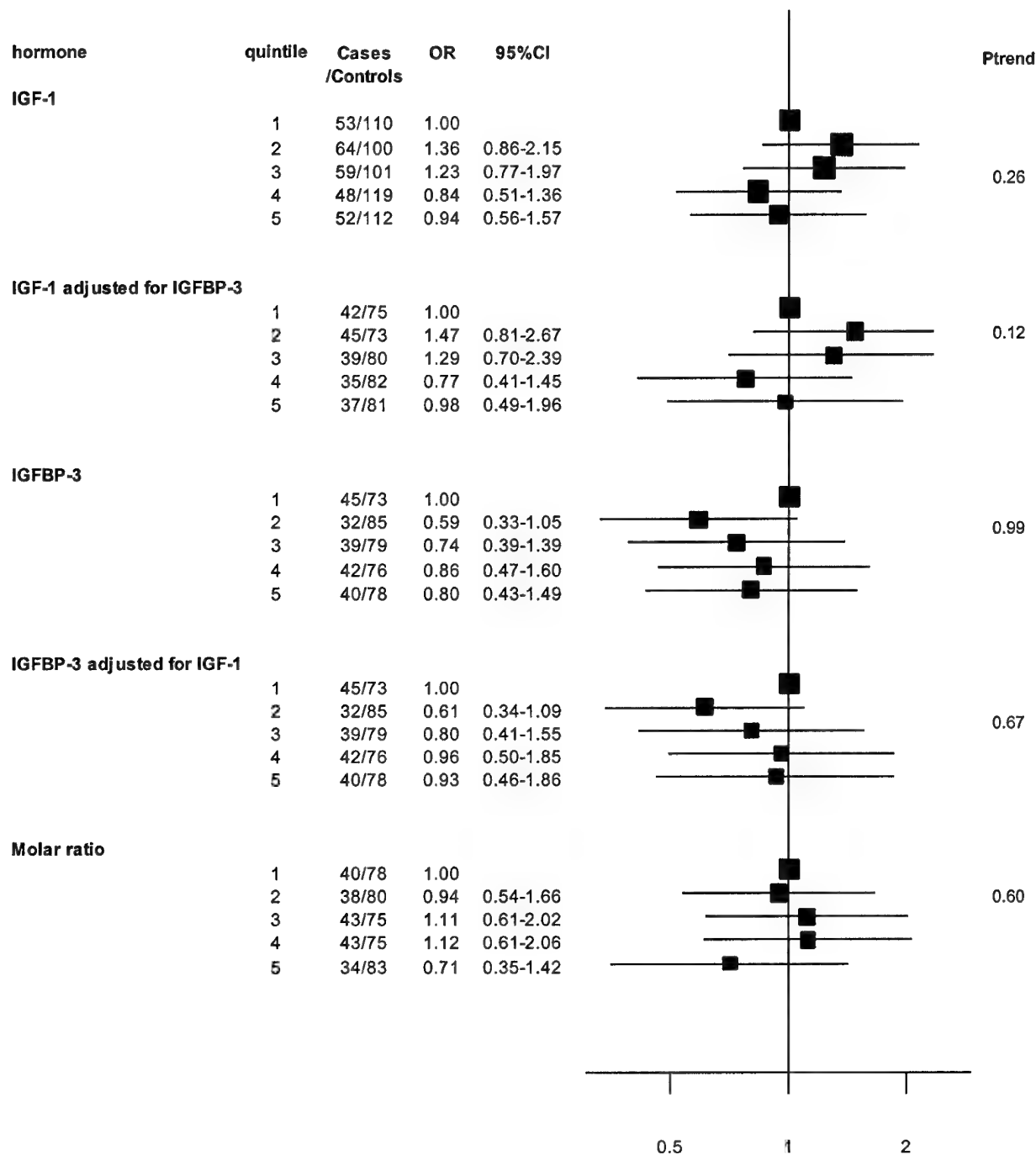
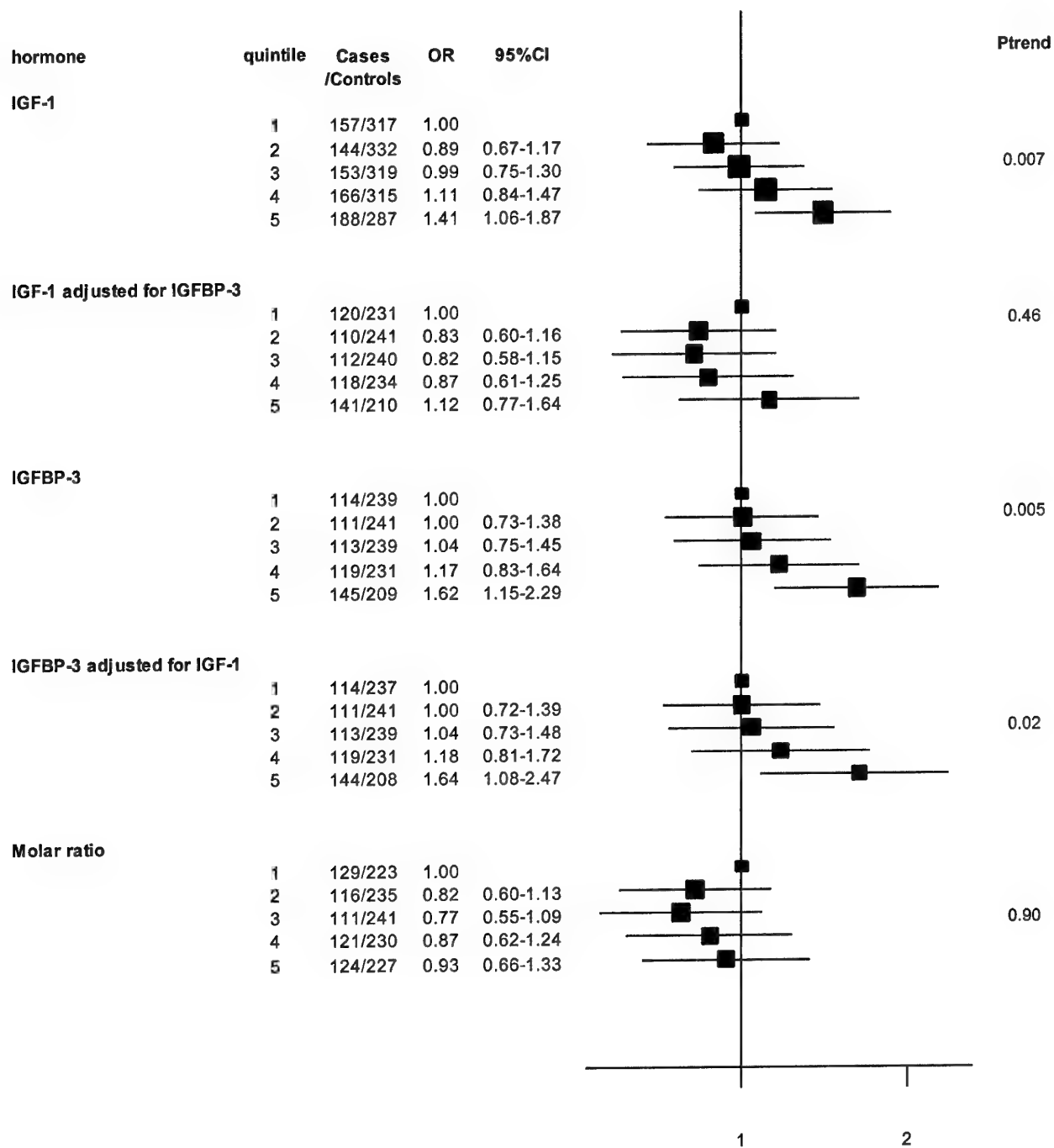
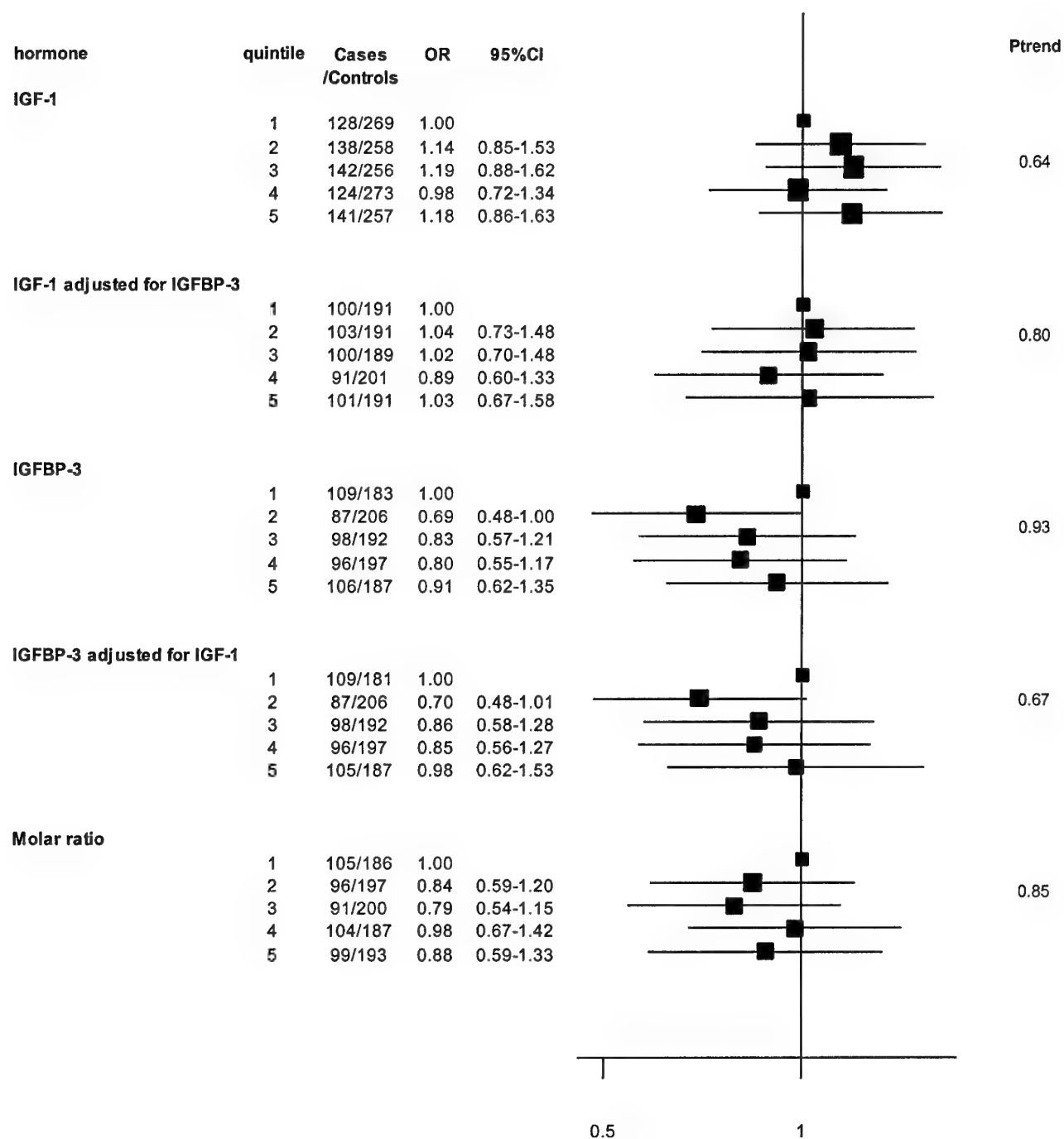


Figure 5. Relative risk of breast cancer among women older than 50 at diagnosis by quintiles of growth hormone levels



**Figure 6. Relative risk of breast cancer among women younger than 60 at diagnosis
by quintiles of growth hormone levels**



**Figure 7. Relative risk of breast cancer among women older than 60 at diagnosis
by quintiles of growth hormone levels**

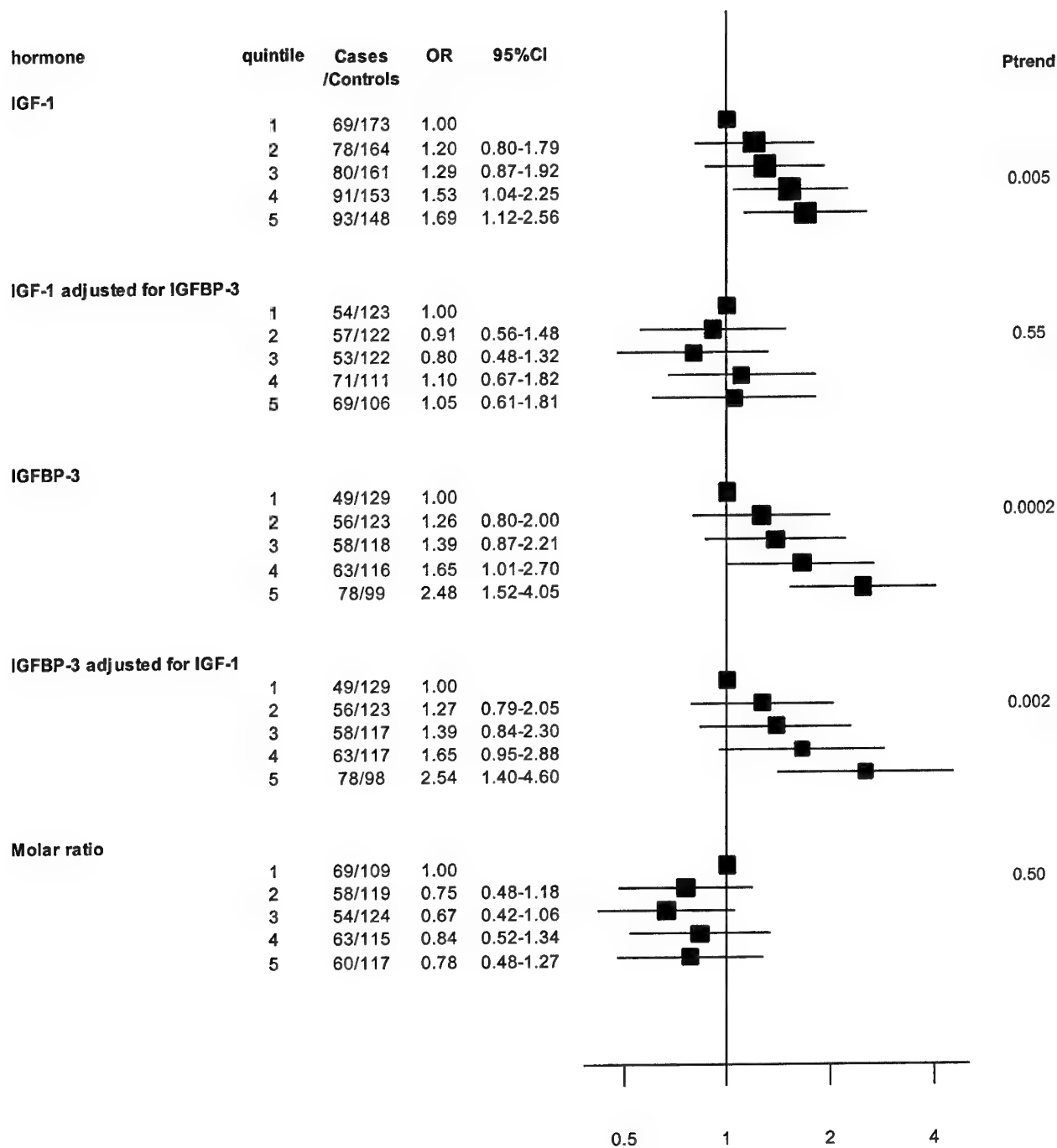


Table 1: Numbers of subjects genotyped for each of the 22 SNPs on 2342 subjects

| SNP | Variables' names | N | N Missing | Frequency Missing |
|----------------------------|----------------------|------|-----------|-------------------|
| 11GHR_M28462_174AG | G11GHRSM28462AG | 2297 | 45 | 1.92 |
| 16GHR_M28466_748AC | G16GHRSM28466AC | 2312 | 30 | 1.28 |
| 24IGF1_X57025_3340AG | G24IGF1SX57025AG | 2314 | 28 | 1.20 |
| 28IGFBP1_M74587_187AG | G28IGFBP1SM74587AG | 2295 | 47 | 2.01 |
| 30IGFBP1_M74587_5110CT | G30IGFBP1SM74587CT | 2317 | 25 | 1.07 |
| 31IGFBP1_M74587_5179GA | G31IGFBP1SM74587GA | 2322 | 20 | 0.85 |
| 33IGFBP3_M35878_5709GC | G33IGFBP3SM35878GC | 2289 | 53 | 2.26 |
| 36IGFBP3_M35878_8291CT | G36IGFBP3SM35878CT | 2322 | 20 | 0.85 |
| 38IGFBP3_M35878_9156AG | G38IGFBP3SM35878AG | 2327 | 15 | 0.64 |
| 39IGFBP3_M35878_10049AAG | G39IGFBP3SM35878AAG | 2311 | 31 | 1.32 |
| 40SST_J00306_1399TC | G40SSTJ00306TC | 2302 | 40 | 1.71 |
| 46SSTR3_M96738_889GA | G46SSTR3SM96738GA | 2298 | 44 | 1.88 |
| 53SSTR5_D16827_192CA | G53SSTR5SD16827CA | 2318 | 24 | 1.02 |
| 56GHRELIN_AC008116_48106AG | G56GHRELINAC008116AG | 2303 | 39 | 1.67 |
| 57GHRELIN_AC008116_48002AC | G57GHRELINAC008116AC | 2325 | 17 | 0.73 |
| 58GHRELIN_AF269558_3857AT | G58GHRELINAF269558AT | 2312 | 30 | 1.28 |
| 59GHRELIN_AF296558_4060GT | G59GHRELINAF296558GT | 2278 | 64 | 2.73 |
| 66GHRHR_AC005155_58474AG | G66GHRHRAC005155AG | 2329 | 13 | 0.56 |
| 69GHRHR_AC005155_63007GA | G69GHRHRAC005155GA | 2317 | 25 | 1.07 |
| 72GHRHR_AC005155_64092GC | G72GHRHRAC005155GC | 2318 | 24 | 1.02 |
| 73GHRH_AL031659_91261TC | G73GHRHSAL031659TC | 2315 | 27 | 1.15 |
| 75SSTR4_D16826_900GT | G75SSTR4SD16826GT | 2304 | 38 | 1.62 |

Table 2: For each SNP, numbers of observations, means of IGF-I by category of polymorphisms (homozygotes 1st allele, heterozygotes, homozygotes 2nd allele), p-values, R-square and R-square adjusted of different models with IGF-I as dependent variable (codominant model, dominant 1st allele, dominant 2nd allele) and average excess p-values of IGF-I

| Gene | SNP | NObs | Mean1 (Nobs) | Mean2 (Nobs) | Mean3 (Nobs) | Codominant model | | | Dominant model 1 st allele | | | Dominant model 2 nd allele | | | Average Excess p-value |
|---------|-----------------------|------|-----------------|-----------------|-----------------|------------------|---------|----------|--|---------|----------|--|---------|----------|------------------------------|
| | | | | | | Pvalue | Rsqr | Rsqr Adj | Pvalue | Rsqr | Rsqr Adj | Pvalue | Rsqr | Rsqr Adj | |
| GHR | G11GHRSM28462AG | 2296 | 240.9 (198) | 240.5 (922) | 239.3 (1176) | 0.70 | 0.00007 | 0.000000 | 0.69 | 0.00007 | 0.000000 | 0.85 | 0.00002 | 0.000000 | 0.67 |
| | G16GHRSM28466AC | 2311 | 239.8 (681) | 240.4 (1093) | 235.6 (537) | 0.37 | 0.00034 | 0.000000 | 0.22 | 0.00063 | 0.000201 | 0.77 | 0.00004 | 0.000000 | 0.81 |
| IGF1 | G24IGF1SX57025AG | 2313 | 239.2 (401) | 238.7 (1114) | 240.5 (798) | 0.72 | 0.00006 | 0.000000 | 0.62 | 0.00010 | 0.000000 | 0.96 | 0.00000 | 0.000000 | 0.36 |
| IGFBP1 | G28IGFBP1SM74587AG | 2294 | 240.0 (320) | 238.6 (1098) | 239.7 (876) | 0.95 | 0.00000 | 0.000000 | 0.82 | 0.00002 | 0.000000 | 0.85 | 0.00002 | 0.000000 | 0.45 |
| | G30IGFBP1SM74587CT | 2316 | 239.0 (2134) | 242.4 (174) | 204.9 (8) | 0.99 | 0.00000 | 0.000000 | 0.21 | 0.00069 | 0.000254 | 0.77 | 0.00004 | 0.000000 | 0.49 |
| | G31IGFBP1SM74587GA | 2321 | 239.1 (262) | 237.2 (1042) | 241.2 (1017) | 0.40 | 0.00030 | 0.000000 | 0.26 | 0.00054 | 0.000113 | 0.99 | 0.00000 | 0.000000 | 0.20 |
| | G33IGFBP3SM35878GC | 2288 | 246.0 (99) | 241.3 (762) | 236.9 (1427) | 0.11 | 0.00112 | 0.000687 | 0.13 | 0.00098 | 0.000546 | 0.34 | 0.00040 | 0.000000 | 0.05 |
| SST | G36IGFBP3SM35878CT | 2321 | 238.7 (2282) | 279.2 (39) | | 0.001 | 0.00458 | 0.004151 | | 0.00000 | 0.000000 | 0.001 | 0.00458 | 0.004151 | <0.01 |
| | G38IGFBP3SM35878AG | 2326 | 239.0 (1506) | 239.4 (734) | 240.6 (86) | 0.85 | 0.00002 | 0.000000 | 0.87 | 0.00001 | 0.000000 | 0.88 | 0.00001 | 0.000000 | 0.42 |
| | G39IGFBP3SM35878AAG | 2310 | 240.1 (1693) | 236.1 (577) | 234.3 (40) | 0.25 | 0.00057 | 0.000140 | 0.70 | 0.00007 | 0.000000 | 0.25 | 0.00058 | 0.000143 | 0.88 |
| | G40SSTR3J00306TC | 2301 | 240.5 (1859) | 232.8 (418) | 246.7 (24) | 0.15 | 0.00092 | 0.000488 | 0.63 | 0.00010 | 0.000000 | 0.09 | 0.00126 | 0.000825 | 0.06 |
| SSTR3 | G46SSTR3SM96738GA | 2297 | 238.5 (1455) | 240.3 (729) | 243.8 (113) | 0.42 | 0.00029 | 0.000000 | 0.52 | 0.00018 | 0.000000 | 0.48 | 0.00021 | 0.000000 | 0.23 |
| SSTR5 | G53SSTR5SD16827CA | 2317 | 240.0 (2057) | 233.7 (255) | 187.1 (5) | 0.11 | 0.00110 | 0.000667 | 0.13 | 0.00099 | 0.000559 | 0.16 | 0.00087 | 0.000439 | 0.05 |
| GHRELIN | G56GHRELINSA008116AG | 2302 | 239.8 (801) | 236.8 (1111) | 243.2 (390) | 0.71 | 0.00006 | 0.000000 | 0.23 | 0.00062 | 0.000187 | 0.69 | 0.00007 | 0.000000 | 0.35 |
| | G57GHRELINSA008116AC | 2324 | 240.8 (1070) | 237.2 (1012) | 239.8 (242) | 0.51 | 0.00019 | 0.000000 | 0.89 | 0.00001 | 0.000000 | 0.34 | 0.00040 | 0.000000 | 0.73 |
| | G58GHRELINSAF269558AT | 2311 | 239.1 (2027) | 238.1 (273) | 247.6 (11) | 0.96 | 0.00000 | 0.000000 | 0.71 | 0.00006 | 0.000000 | 0.90 | 0.00001 | 0.000000 | 0.52 |
| | G59GHRELINSAF296558GT | 2277 | 242.4 (645) | 237.4 (1080) | 238.9 (552) | 0.39 | 0.00032 | 0.000000 | 0.92 | 0.00001 | 0.000000 | 0.20 | 0.00071 | 0.000273 | 0.81 |
| GHRHR | G66GHRHRSA0005155AG | 2328 | 240.5 (1252) | 238.8 (916) | 230.9 (160) | 0.19 | 0.00073 | 0.000305 | 0.16 | 0.00085 | 0.000423 | 0.36 | 0.00036 | 0.000000 | 0.91 |
| | G69GHRHRSA0005155GA | 2316 | 239.2 (1853) | 239.6 (439) | 222.3 (24) | 0.72 | 0.00006 | 0.000000 | 0.28 | 0.00050 | 0.000069 | 0.91 | 0.00001 | 0.000000 | 0.63 |
| | G72GHRHRSA0005155GC | 2317 | 239.8 (1121) | 239.3 (985) | 235.4 (211) | 0.54 | 0.00016 | 0.000000 | 0.46 | 0.00024 | 0.000000 | 0.71 | 0.00006 | 0.000000 | 0.74 |
| GHRH | G73GHRHSAL031659TC | 2314 | 238.8 (2218) | 247.5 (96) | | 0.28 | 0.00051 | 0.000075 | | 0.00000 | 0.000000 | 0.28 | 0.00051 | 0.000075 | 0.11 |
| SSTR4 | G75SSTR4SD16826GT | 2303 | 240.4 (359) | 241.1 (1094) | 236.0 (850) | 0.22 | 0.00065 | 0.000213 | 0.14 | 0.00097 | 0.000531 | 0.73 | 0.00005 | 0.000000 | 0.90 |

Table 3: For each SNP, numbers of observations, means of IGFBP3 by category of polymorphisms (homozygotes 1st allele, heterozygotes 2nd allele), p-values, R-square and R-square adjusted of different models with IGFBP3 as dependent variable (codominant model, dominant 1st allele, dominant 2nd allele) and average excess p-values of IGFBP3

| Gene | SNP | NObs | Mean1 (Nobs) | Mean2 (Nobs) | Mean3 (Nobs) | Codominant model | | | Dominant model 1 st allele | | | Dominant model 2 nd allele | | | Average Excess p-value |
|---------|-----------------------|------|-----------------|-----------------|-----------------|------------------|---------|----------|--|---------|----------|--|---------|----------|------------------------------|
| | | | | | | Pvalue | Rsq | Rsq Adj | Pvalue | Rsq | Rsq Adj | Pvalue | Rsq | Rsq Adj | |
| GHR | G11GHRSM28462AG | 2292 | 2939 (196) | 3003 (920) | 2956 (1176) | 0.54 | 0.00017 | 0.000000 | 0.23 | 0.00063 | 0.000192 | 0.47 | 0.00023 | 0.000000 | 0.73 |
| | G16GHRSM28466AC | 2308 | 2953 (680) | 2988 (1092) | 2964 (536) | 0.73 | 0.00005 | 0.000000 | 0.75 | 0.00004 | 0.000000 | 0.40 | 0.00031 | 0.000000 | 0.35 |
| IGF1 | G24IGFISX57025AG | 2309 | 2966 (399) | 2956 (1113) | 3005 (797) | 0.25 | 0.00058 | 0.000142 | 0.14 | 0.00096 | 0.000524 | 0.79 | 0.00003 | 0.000000 | 0.08 |
| IGFBP1 | G28IGFBPISM74587AG | 2290 | 2949 (318) | 2991 (1096) | 2965 (876) | 0.97 | 0.00000 | 0.000000 | 0.57 | 0.00014 | 0.000000 | 0.47 | 0.00023 | 0.000000 | 0.51 |
| | G30IGFBPISM74587CT | 2312 | 2967 (2130) | 3029 (174) | 3268 (8) | 0.14 | 0.00096 | 0.000530 | 0.24 | 0.00061 | 0.000176 | 0.18 | 0.00077 | 0.000334 | 0.06 |
| | G31IGFBPISM74587GA | 2317 | 2941 (260) | 2977 (1041) | 2978 (1016) | 0.56 | 0.00015 | 0.000000 | 0.78 | 0.00003 | 0.000000 | 0.43 | 0.00027 | 0.000000 | 0.30 |
| | G33IGFBP3SM35878GC | 2284 | 2741 (99) | 2928 (760) | 3014 (1425) | <.0001 | 0.00758 | 0.007146 | 0.0004 | 0.00545 | 0.005010 | 0.001 | 0.00492 | 0.004487 | <0.001 |
| SST | G36IGFBP3SM35878CT | 2317 | 2977 (2278) | 2777 (39) | | 0.08 | 0.00134 | 0.000905 | | 0.00000 | | 0.08 | 0.00134 | 0.000905 | 0.04 |
| | G38IGFBP3SM35878AG | 2322 | 2979 (1505) | 2954 (731) | 3020 (86) | 0.78 | 0.00003 | 0.000000 | 0.53 | 0.00017 | 0.000000 | 0.57 | 0.00014 | 0.000000 | 0.61 |
| | G39IGFBP3SM35878AAG | 2306 | 2962 (1691) | 3002 (575) | 3044 (40) | 0.18 | 0.00078 | 0.000344 | 0.52 | 0.00018 | 0.000000 | 0.20 | 0.00072 | 0.000285 | 0.09 |
| | G40SSTSJ00306TC | 2297 | 2967 (1856) | 2998 (417) | 2880 (24) | 0.65 | 0.00009 | 0.000000 | 0.52 | 0.00018 | 0.000000 | 0.51 | 0.00019 | 0.000000 | 0.32 |
| SSTR3 | G46SSTR3SM96738GA | 2293 | 2979 (1453) | 2966 (728) | 2959 (112) | 0.65 | 0.00009 | 0.000000 | 0.83 | 0.00002 | 0.000000 | 0.65 | 0.00009 | 0.000000 | 0.68 |
| | G53SSTR5SD16827CA | 2313 | 2974 (2053) | 2977 (255) | 2737 (5) | 0.88 | 0.00001 | 0.000000 | 0.45 | 0.00025 | 0.000000 | 0.97 | 0.00000 | 0.000000 | 0.55 |
| GHRELIN | G56GHRELINSAC008116AG | 2298 | 2998 (800) | 2962 (1109) | 2976 (389) | 0.46 | 0.00024 | 0.000000 | 0.98 | 0.00000 | 0.000000 | 0.29 | 0.00049 | 0.000053 | 0.73 |
| | G57GHRELINSAC008116AC | 2320 | 2975 (1067) | 2952 (1010) | 3064 (243) | 0.35 | 0.00038 | 0.000000 | 0.04 | 0.00188 | 0.001452 | 0.97 | 0.00000 | 0.000000 | 0.18 |
| | G58GHRELINSAC008116AT | 2307 | 2968 (2024) | 3002 (272) | 3011 (11) | 0.44 | 0.00026 | 0.000000 | 0.85 | 0.00002 | 0.000000 | 0.44 | 0.00026 | 0.000000 | 0.23 |
| | G59GHRELINSAC008116GT | 2273 | 3021 (645) | 2980 (1078) | 2916 (550) | 0.01 | 0.00287 | 0.002426 | 0.02 | 0.00235 | 0.001910 | 0.06 | 0.00159 | 0.001152 | 0.02 |
| GHRHR | G66GHRHRAC005155AG | 2324 | 2970 (1250) | 2958 (916) | 3078 (158) | 0.34 | 0.00039 | 0.000000 | 0.05 | 0.00164 | 0.001214 | 0.85 | 0.00002 | 0.000000 | 0.18 |
| | G69GHRHRAC005155GA | 2312 | 2970 (1850) | 2989 (438) | 2912 (24) | 0.78 | 0.00003 | 0.000000 | 0.67 | 0.00008 | 0.000000 | 0.68 | 0.00007 | 0.000000 | 0.41 |
| | G72GHRHRAC005155GC | 2313 | 2964 (1120) | 2966 (984) | 3052 (209) | 0.22 | 0.00064 | 0.000208 | 0.09 | 0.00127 | 0.000833 | 0.55 | 0.00015 | 0.000000 | 0.11 |
| | G73GHRHRAC005155TC | 2310 | 2970 (2214) | 3006 (96) | | 0.62 | 0.00010 | 0.000000 | | 0.00000 | | 0.62 | 0.00010 | 0.000000 | 0.31 |
| SSTR4 | G75SSTR4SD16826GT | 2299 | 2978 (358) | 2978 (1092) | 2965 (849) | 0.71 | 0.00006 | 0.000000 | 0.67 | 0.00008 | 0.000000 | 0.89 | 0.00001 | 0.000000 | 0.66 |

Table 4: Number of SNPs per gene, R-square adjusted of full rank haplotype models and results of stepwise regression models

| Gene | Number of SNPs | R ² adj of full rank ("maximum") haplotype model (Rsq) | | Result from stepwise regression: Nr of SNP loci showing effects / model p-value / model R ² adj (Rsq) | |
|--------|----------------|--|----------------|---|---|
| | | IGF-1 | IGFBP-3 | IGF-1 | IGFBP-3 |
| GHR | 2 | 0.0000 (.0006) | 0.0004 (.002) | / | / |
| IGF1 | 1 | 0.0000 (.0001) | 0.0005 (.001) | / | / |
| IGFBP1 | 3 | 0.0000 (.002) | 0.0004 (.002) | / | / |
| IGFBP3 | 4 | 0.003 (.006) | 0.007 (.0103) | 1 / p=.001 / R ² =(.0005).004 | 1 / p=.001 / R ² =(.008).007 |
| SST | 1 | 0.0008 (.001) | 0.0000 (.0005) | / | / |
| SSTR3 | 1 | 0.0000 (.0003) | 0.0000 (.0001) | / | / |
| SSTR5 | 1 | 0.0008 (.002) | 0.0000 (.0001) | / | / |
| GHRIN | 4 | 0.0000 (.002) | 0.0035 (.007) | 2 / p=.02 / R ² =(.008).004 | 2 / p=.01 / R ² =(.005).003 |
| GHRHR | 3 | 0.0000 (.002) | 0.0000 (.002) | / | / |
| GHRH | 1 | 0.0001 (.0005) | 0.0000 (.0001) | / | / |
| SSTR4 | 1 | 0.0005 (.001) | 0.0000 (.0001) | / | / |

Codominant model

Table 5: For each SNP, numbers of cases and controls by category of polymorphisms (homozygotes 1st allele, heterozygotes, homozygotes 2nd allele), hazard ratios, confidence intervals and p-values associated, means of IGF-I and IGFBP3 and p-values of the mean's tests

| Gene | Variable | cases | controls | n | HazardRatio | HRLowerCL | HRUpperCL | ProbChiSq | IGF1 mean | ProbF | IGFBP3 mean | ProbF |
|--------|----------|-------|----------|------|-------------|-----------|-----------|-----------|-----------|--------|-------------|--------|
| GHR | G11 | 779 | 1507 | 2286 | . | . | . | 0.6952 | . | 0.8366 | . | 0.2887 |
| | G111 | 61 | 138 | 199 | . | . | . | . | 240.613 | . | 2940.60 | . |
| | G112 | 322 | 601 | 923 | 1.207 | 0.869 | 1.677 | 0.2620 | 240.995 | . | 3001.12 | . |
| | G113 | 396 | 768 | 1164 | 1.158 | 0.837 | 1.603 | 0.3753 | 239.023 | . | 2957.27 | . |
| GHR | G16 | 774 | 1517 | 2291 | . | . | . | 0.9917 | . | 0.4771 | . | 0.6211 |
| | G161 | 219 | 454 | 673 | . | . | . | . | 239.862 | . | 2953.04 | . |
| | G162 | 387 | 708 | 1095 | 1.139 | 0.925 | 1.402 | 0.2202 | 240.740 | . | 2986.75 | . |
| | G163 | 168 | 355 | 523 | 0.982 | 0.766 | 1.259 | 0.8877 | 235.851 | . | 2976.15 | . |
| IGF1 | G24 | 774 | 1521 | 2295 | . | . | . | 0.2417 | . | 0.5469 | . | 0.2918 |
| | G241 | 131 | 271 | 402 | . | . | . | . | 238.896 | . | 2982.14 | . |
| | G242 | 364 | 749 | 1113 | 0.999 | 0.783 | 1.273 | 0.9913 | 238.215 | . | 2955.57 | . |
| | G243 | 279 | 501 | 780 | 1.133 | 0.879 | 1.460 | 0.3357 | 242.073 | . | 3007.18 | . |
| IGFBP1 | G28 | 770 | 1497 | 2267 | . | . | . | 0.7454 | . | 0.8628 | . | 0.4479 |
| | G281 | 114 | 208 | 322 | . | . | . | . | 240.002 | . | 2946.05 | . |
| | G282 | 353 | 734 | 1087 | 0.871 | 0.671 | 1.131 | 0.2992 | 238.277 | . | 2993.69 | . |
| | G283 | 303 | 555 | 858 | 0.981 | 0.751 | 1.281 | 0.8865 | 240.044 | . | 2961.21 | . |
| IGFBP1 | G30 | 776 | 1524 | 2300 | . | . | . | 0.7178 | . | 0.4384 | . | 0.2107 |
| | G301 | 712 | 1407 | 2119 | . | . | . | . | 239.301 | . | 2967.49 | . |
| | G302 | 62 | 111 | 173 | 1.110 | 0.799 | 1.543 | 0.5330 | 240.550 | . | 3041.25 | . |
| | G303 | 2 | 6 | 8 | 0.667 | 0.135 | 3.303 | 0.6197 | 204.883 | . | 3267.95 | . |
| IGFBP1 | G31 | 780 | 1533 | 2313 | . | . | . | 0.7641 | . | 0.3612 | . | 0.6120 |
| | G311 | 89 | 175 | 264 | . | . | . | . | 239.072 | . | 2934.10 | . |
| | G312 | 345 | 693 | 1038 | 0.977 | 0.733 | 1.303 | 0.8739 | 236.931 | . | 2979.98 | . |
| | G313 | 346 | 665 | 1011 | 1.019 | 0.762 | 1.362 | 0.8988 | 241.774 | . | 2980.28 | . |

Codominant model

| Gene | Variable | cases | controls | n | HazardRatio | HRLowerCL | HRUpperCL | ProbChISq | IGF1 mean | ProbF | IGFBP3 mean | ProbF |
|--------|----------|-------|----------|------|-------------|-----------|-----------|-----------|-----------|--------|-------------|--------|
| IGFBP3 | G33 | 767 | 1489 | 2256 | . | . | . | 0.9793 | . | 0.2275 | . | <.0001 |
| | G331 | 38 | 59 | 97 | . | . | . | . | 246.473 | . | 2708.65 | . |
| | G332 | 247 | 506 | 753 | 0.763 | 0.493 | 1.183 | 0.2270 | 241.850 | . | 2924.81 | . |
| | G333 | 482 | 924 | 1406 | 0.824 | 0.540 | 1.258 | 0.3702 | 236.949 | . | 3022.11 | . |
| IGFBP3 | G36 | 776 | 1529 | 2305 | . | . | . | 0.3330 | . | 0.0019 | . | 0.0584 |
| | G361 | 766 | 1501 | 2267 | . | . | . | . | 238.807 | . | 2977.93 | . |
| | G362 | 10 | 28 | 38 | 0.700 | 0.340 | 1.442 | 0.3330 | 277.659 | . | 2759.58 | . |
| | G363 | . | . | . | . | . | . | . | . | . | . | . |
| IGFBP3 | G38 | 782 | 1540 | 2322 | . | . | . | 0.1892 | . | 0.9739 | . | 0.7130 |
| | G381 | 521 | 980 | 1501 | . | . | . | . | 239.216 | . | 2980.09 | . |
| | G382 | 234 | 501 | 735 | 0.880 | 0.727 | 1.065 | 0.1900 | 239.219 | . | 2957.79 | . |
| | G383 | 27 | 59 | 86 | 0.871 | 0.549 | 1.383 | 0.5588 | 241.154 | . | 3006.51 | . |
| IGFBP3 | G39 | 778 | 1520 | 2298 | . | . | . | 0.5523 | . | 0.4213 | . | 0.3914 |
| | G391 | 563 | 1115 | 1678 | . | . | . | . | 240.555 | . | 2964.44 | . |
| | G392 | 201 | 379 | 580 | 1.059 | 0.864 | 1.299 | 0.5787 | 235.856 | . | 3009.31 | . |
| | G393 | 14 | 26 | 40 | 1.092 | 0.569 | 2.095 | 0.7916 | 235.352 | . | 3014.71 | . |
| SST | G40 | 775 | 1510 | 2285 | . | . | . | 0.0454 | . | 0.1040 | . | 0.4577 |
| | G401 | 608 | 1241 | 1849 | . | . | . | . | 240.855 | . | 2965.64 | . |
| | G402 | 158 | 255 | 413 | 1.251 | 1.001 | 1.562 | 0.0487 | 232.159 | . | 3006.97 | . |
| | G403 | 9 | 14 | 23 | 1.311 | 0.565 | 3.043 | 0.5283 | 246.274 | . | 2876.80 | . |
| SSTR3 | G46 | 772 | 1501 | 2273 | . | . | . | 0.8182 | . | 0.6986 | . | 0.9457 |
| | G461 | 491 | 945 | 1436 | . | . | . | . | 238.638 | . | 2976.59 | . |
| | G462 | 243 | 483 | 726 | 0.970 | 0.803 | 1.172 | 0.7527 | 240.654 | . | 2965.80 | . |
| | G463 | 38 | 73 | 111 | 0.996 | 0.662 | 1.498 | 0.9829 | 243.924 | . | 2974.45 | . |

Codominant model

| Gene | Variable | cases | controls | n | HazardRatio | HRLowerCL | HRUpperCL | ProbChiSq | IGF1 mean | ProbF | IGFBP3 mean | ProbF |
|-------|----------|-------|----------|------|-------------|-----------|-----------|-----------|-----------|--------|-------------|--------|
| GHRHR | G69 | 775 | 1525 | 2300 | . | . | . | 0.2928 | . | 0.6572 | . | 0.9420 |
| | G691 | 608 | 1220 | 1828 | . | . | . | . | 239.143 | . | 2971.99 | . |
| | G692 | 157 | 292 | 449 | 1.078 | 0.870 | 1.336 | 0.4917 | 240.066 | . | 2981.98 | . |
| | G693 | 10 | 13 | 23 | 1.559 | 0.683 | 3.559 | 0.2916 | 225.122 | . | 2941.37 | . |
| GHRHR | G72 | 775 | 1526 | 2301 | . | . | . | 0.0705 | . | 0.6981 | . | 0.2317 |
| | G721 | 392 | 723 | 1115 | . | . | . | . | 240.186 | . | 2969.26 | . |
| | G722 | 322 | 651 | 973 | 0.910 | 0.758 | 1.092 | 0.3091 | 239.523 | . | 2960.21 | . |
| | G723 | 61 | 152 | 213 | 0.753 | 0.549 | 1.034 | 0.0792 | 235.330 | . | 3050.88 | . |
| GHRH | G73 | 776 | 1522 | 2298 | . | . | . | 0.5009 | . | 0.2513 | . | 0.5514 |
| | G731 | 741 | 1462 | 2203 | . | . | . | . | 238.711 | . | 2968.93 | . |
| | G732 | 35 | 60 | 95 | 1.160 | 0.753 | 1.787 | 0.5009 | 247.932 | . | 3012.96 | . |
| | G733 | . | . | . | . | . | . | . | . | . | . | . |
| SSTR4 | G75 | 765 | 1501 | 2266 | . | . | . | 0.7021 | . | 0.3180 | . | 0.9147 |
| | G751 | 112 | 242 | 354 | . | . | . | . | 240.398 | . | 2987.89 | . |
| | G752 | 377 | 710 | 1087 | 1.172 | 0.905 | 1.517 | 0.2283 | 241.032 | . | 2972.68 | . |
| | G753 | 276 | 549 | 825 | 1.105 | 0.841 | 1.451 | 0.4742 | 235.834 | . | 2969.07 | . |

[illegible]

[illegible]

Dominant model 1st allele

| Gene | Variable | cases | controls | n | HazardRatio | HRLowerCL | HRUpperCL | ProbChiSq | IGF1 mean | ProbF | IGFBP3 mean | ProbF |
|---------|----------|-------|----------|------|-------------|-----------|-----------|-----------|--------------|--------|----------------|--------|
| GHRELIN | G59 | 759 | 1469 | 2228 | . | . | . | 0.2408 | . | 0.6613 | . | 0.0096 |
| | G591 | 172 | 364 | 536 | . | . | . | . | 238.166 | . | 2909.03 | . |
| | G592 | 587 | 1105 | 1692 | 1.129 | 0.922 | 1.382 | 0.2408 | 239.820 | . | 2999.77 | . |
| GHRHR | G66 | 782 | 1541 | 2323 | . | . | . | 0.2884 | . | 0.1205 | . | 0.0758 |
| | G661 | 47 | 111 | 158 | . | . | . | . | 230.077 | . | 3071.33 | . |
| | G662 | 735 | 1430 | 2165 | 1.208 | 0.852 | 1.712 | 0.2884 | 239.880 | . | 2966.97 | . |
| GHRHR | G69 | 775 | 1525 | 2300 | . | . | . | 0.3057 | . | 0.3750 | . | 0.8263 |
| | G691 | 10 | 13 | 23 | . | . | . | . | 225.122 | . | 2941.37 | . |
| | G692 | 765 | 1512 | 2277 | 0.650 | 0.285 | 1.482 | 0.3057 | 239.325 | . | 2973.96 | . |
| GHRHR | G72 | 775 | 1526 | 2301 | . | . | . | 0.1222 | . | 0.4096 | . | 0.0920 |
| | G721 | 61 | 152 | 213 | . | . | . | . | 235.330 | . | 3050.88 | . |
| | G722 | 714 | 1374 | 2088 | 1.273 | 0.937 | 1.728 | 0.1222 | 239.877 | . | 2965.05 | . |
| SSTR4 | G75 | 765 | 1501 | 2266 | . | . | . | 0.7927 | . | 0.1316 | . | 0.8127 |
| | G751 | 276 | 549 | 825 | . | . | . | . | 235.834 | . | 2969.07 | . |
| | G752 | 489 | 952 | 1441 | 1.025 | 0.854 | 1.230 | 0.7927 | 240.876 | . | 2976.42 | . |

Dominant model 2nd allele

[illegible]

Dominant model 2nd allele

| Gene | Variable | cases | controls | n | HazardRatio | HRLowerCL | HRUpperCL | ProbChiSq | IGF1 mean | Probf | IGFBP3 mean | Probf |
|---------|----------|-------|----------|------|-------------|-----------|-----------|-----------|--------------|--------|----------------|--------|
| GHRELIN | G58 | 773 | 1518 | 2291 | . | . | . | 0.0301 | . | 0.7821 | . | 0.3923 |
| | G581 | 662 | 1347 | 2009 | . | . | . | . | 239.290 | . | 2969.32 | . |
| | G582 | 111 | 171 | 282 | 1.329 | 1.028 | 1.718 | 0.0301 | 237.943 | . | 3007.95 | . |
| GHRELIN | G59 | 759 | 1469 | 2228 | . | . | . | 0.9215 | . | 0.1416 | . | 0.0514 |
| | G591 | 217 | 419 | 636 | . | . | . | . | 243.175 | . | 3024.12 | . |
| | G592 | 542 | 1050 | 1592 | 0.990 | 0.817 | 1.201 | 0.9215 | 237.923 | . | 2959.52 | . |
| GHRHR | G66 | 782 | 1541 | 2323 | . | . | . | 0.3530 | . | 0.1785 | . | 0.8858 |
| | G661 | 433 | 822 | 1255 | . | . | . | . | 241.186 | . | 2975.90 | . |
| | G662 | 349 | 719 | 1068 | 0.922 | 0.777 | 1.094 | 0.3530 | 236.891 | . | 2971.67 | . |
| GHRHR | G69 | 775 | 1525 | 2300 | . | . | . | 0.3786 | . | 0.9609 | . | 0.8272 |
| | G691 | 608 | 1220 | 1828 | . | . | . | . | 239.143 | . | 2971.99 | . |
| | G692 | 167 | 305 | 472 | 1.099 | 0.891 | 1.355 | 0.3786 | 239.336 | . | 2980.00 | . |
| GHRHR | G72 | 775 | 1526 | 2301 | . | . | . | 0.1422 | . | 0.6575 | . | 0.8091 |
| | G721 | 392 | 723 | 1115 | . | . | . | . | 240.186 | . | 2969.26 | . |
| | G722 | 383 | 803 | 1186 | 0.879 | 0.739 | 1.044 | 0.1422 | 238.768 | . | 2976.36 | . |
| GHRH | G73 | 776 | 1522 | 2298 | . | . | . | 0.5009 | . | 0.2513 | . | 0.5514 |
| | G731 | 741 | 1462 | 2203 | . | . | . | . | 238.711 | . | 2968.93 | . |
| | G732 | 35 | 60 | 95 | 1.160 | 0.753 | 1.787 | 0.5009 | 247.932 | . | 3012.96 | . |
| SSTR4 | G75 | 765 | 1501 | 2266 | . | . | . | 0.2827 | . | 0.7164 | . | 0.6834 |
| | G751 | 112 | 242 | 354 | . | . | . | . | 240.398 | . | 2987.89 | . |
| | G752 | 653 | 1259 | 1912 | 1.145 | 0.894 | 1.466 | 0.2827 | 238.788 | . | 2971.12 | . |